REMARKS

Claims 18-20, 24 and 26-29 were rejected under 25 USC 112. Claim 28 has been amended to recite that the brush means comprises bristles having sufficient stiffness. It is believed this is consistent with the description contained in related applications of the structure and is in compliance with 35 USC 112.

With regard to the rejection of claim 27, it is noted that claim 27 is dependent upon 28 in that once the most atypical cells are isolated, other molecular diagnostic techniques can be performed in addition to or instead of DNA ploidy analysis. It is thus believed claim 27 is compliant with 35 USC 112.

With regard to amended claim 28, the disclosure of '218 and '219 (issued patents 6,297,044 and 6,284,482) incorporated by reference into this application provides sufficient disclosure so as to render the term "most suspect" definite. Please note also that claims have been amended to recite that that which is sought is the "most atypical appearing" as opposed to "most suspect." It is believed to one of ordinary skill in the art this is definite. The specification in those issued patents describes a primary and secondary classifier. The candidate cells of those groups are sent to a neural net "for scoring, and the *highest ranking objects* from the combined two groups are displayed to the expert viewer." The term "highest ranking objects" is another way of saying the "most suspect" or "most atypical appearing" cells and as such complies with 35 USC 112.

The remaining claims were rejected under 35 USC 103 over a combination of Lee '899, Lonky '044 as well as other cited references.

As a preliminary matter, an explanation of how the current invention utilizes DNA ploidy analysis and how this invention is distinct from and improves upon prior practices is set forth.

Prior systems, such as the one raised in the Lee reference ('899), look at particular cells which have already been found to be cytologically or histologically atypical. These atypical cells are then further analyzed for atypical ploidy. This approach has a deficiency in that subtle changes may be missed on the border between negative and atypical. In other words, a cell that is not conclusively cytologically and histologically atypical may still exhibit atypical ploidy. Such a cell may

be in the early stages of advancing into a cytologically and histologically atypical cell, yet in the prior practice would be considered to be negative for cellular abnormality.

However, the current invention avoids this problem by generating a ploidy histogram from the *most atypical appearing* cells on the slide. Whether or not there are actually abnormal cells on a given slide, there are always some that appear more abnormal than the rest. This is true for any sample analyzed by the computer in the current invention – even if the specimen is taken from an entirely healthy individual. As such, the computer is highly sensitive to even the slightest morphological change. Unlike Lee ('899) which analyzes cells for specific threshold abnormalities before subjecting those selected abnormal cells for ploidy analysis, the computer in this invention invariably selects the *most atypical appearing* cells for review by a pathologist, and it is these cells upon which a ploidy histogram is based. An obvious benefit of the current invention is that it can detect atypical ploidy at an earlier stage than is taught by the prior art, thereby increasing the sensitivity for identifying those epithelial lesions which will progress to carcinoma.

With respect to the Examiner's rejection of claim 28 under 35 U.S.C. 103(a) based on the combined teachings of Lee ('899) in view of Lonky ('044) we submit that it is not obvious based on those two references to conduct DNA ploidy analysis on the *most atypical appearing* cells within a specimen. In light of this clarification claim 28 has been amended to recite means to conduct DNA ploidy quantization *from the most atypical appearing cells.*

With respect to the examiner's rejection of claim 24 based on Lonky alone, claim 24 contains the limitations of claim 28 and is patentable thereover for the reasons set forth related thereto.

In response to the examiner's rejection of claim 29 (now part of amended claim 28) on the grounds that the three-stage classification taught by the Lee reference meets the "most suspect" limitation of claim 29 we offer the following: The "most suspect" cells in this invention are not the same as the abnormal cells in Lee. As indicated earlier, the cells that are analyzed in this invention are not necessarily abnormal. Rather, they are a group of cells that are the most suspicious appearing in that particular specimen. Unlike the teaching of Lee that strictly finds abnormal cells, this invention invariably comes up

with the "most suspect" appearing cells in any given sample.

With respect to the examiner's rejection of claim 18, the Rutenberg reference is inappropriate. The Rutenberg reference does not teach a method for a computer to make a diagnosis. Rather, in the cited Rutenberg reference, the computer merely ranks a group of cells as the most abnormal and then displays them for a pathologist to make a diagnosis. The only role for the computer in that reference is to select which cells are the most appropriate for the pathologist to view, i.e. to assist the pathologist in extracting only the most suspicious cells from among many thousands in order for the pathologist to make a diagnosis. In the current invention the *most atypical appearing* cells are not displayed for the pathologist to make a diagnosis, but rather to determine which cells are candidates for further computer (DNA ploidy) analysis.

The examiner rejected claim 19 as obvious when combining the references of Rutenberg, Lonky and Bacus. The teaching of Bacus should not be used as a reference against our invention. When generating a DNA ploidy histogram it is essential that it be based upon the best candidate cells. To quote the Bacus reference: "Given their [DNA ploidy histogram's] value, it is important that the data from which the histograms are generated is accurate..." The crux of this invention is to introduce a method of selecting the *best possible cells* to be the basis of a DNA ploidy histogram. This will not only ensure that the histogram is accurate, but also will allow for the detection of abnormal DNA ploidy at an earlier stage. Bacus initially stains the specimen with the Feulgen stain, which specifically binds to the DNA nucleus. An operator then selects cells from among stored images to be included in the DNA ploidy histogram. Claim 19 at issue here, although it is directed to generating a DNA ploidy histogram, it is limited to the methods of independent claim 28. Claim 28 (c) speaks to an imaging apparatus that first selects individual atypical cells from said cell population. As disclosed in the '482 and 6,297,044 patents, incorporated here by reference, the current invention – unlike Bacus who initially stains with Feulgen – as a first step stains the slide with the stain. The stain is one of the best, most widely used stains for assessing cell type and morphology on disaggregated cytological specimens. As such, it is ideal for the accurate selection of cells to be included in the histogram. As a second step, the slide is stained with the Feulgen stain in order to generate the histogram.

With respect to claim 20, since "selecting atypical cells using reference cells chosen from the same population," is limited by claim 28 which is directed to *most atypical appearing cells*, and not atypical cells of the prior art it avoids the prior at as set forth above.

With respect to the examiner's rejection of claim 27, the Hemstreet reference is distinguished from the method in claim 27. Hemstreet teaches that molecular diagnostics can independently be used for cell analysis. However, the combined references raised by the examiner does not render it obvious to use molecular diagnostics only after a group of cells has been labeled as *most atypical* based on their morphology. Claim 28 includes this limitation.

In view of the specific identification of the improvement of this invention as first selecting the most atypical appearing cells which is nowhere found nor suggested in Lee, the combination of Lee and Lonky will not change that which Lee seeks in its analysis.

In view of the above action and comments, an early notice of allowance is respectfully solicited.

Respectfully submitted,
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Related Applications

The present application relates to and is a continuation-in-part of U.S. Nonprovisional Application Serial No. 09/298,218 filed April 23, 1999 ("the '218 application") now issued Patent No. 6,284,482; U.S. Nonprovisional Application Serial No. 09/298,219 filed April 23, 1999 ("the '219 application") now issued Patent No. 6,297,044; and U.S. Provisional Application Serial No. 60/225,186 filed August 14, 2000 ("the '186 application"). The disclosures of those applications are fully incorporated herein by reference.